Neural crest stem cells in melanoma development

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Abstract: PURPOSE OF REVIEW Metastatic melanoma is the most aggressive skin cancer and despite tremendous efforts and considerable progress in clinical treatment of melanoma patients within recent years, it remains a deadly disease. Current treatments affect melanoma cells indiscriminately, while accumulating evidence suggests that melanoma might be a disease of stem cells. This review aims to summarize the important accomplishments in the field and to emphasize the common molecular and cellular mechanisms regulating self-renewal of neural crest stem cells (NCSCs) and melanoma cells. RECENT FINDINGS A growing number of publications highlight the existence of phenotypic and functional similarities between embryonic NCSCs and melanoma cells. These studies provide compelling evidence that the propagation of melanoma cells critically depends on genes instrumental in neural crest development. The example of Sox10 and Rac1 genes provides detailed illustration of how interfering with these important genes for neural crest development can prevent melanoma formation. SUMMARY The development of new therapies, targeting RAF-MEK-ERK pathway, provided major improvements in outcomes for patients with metastatic melanoma; however, acquired resistance followed by tumor recurrence represents a major clinical challenge. The striking parallels between embryonic NCSCs (eNCSCs) and melanoma cells might lead to the development of new targeted therapeutics selectively eliminating cell populations accountable for tumor initiation, progression and relapse.

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Hide Cover

[MELANOMA AND OTHER SKIN NEOPLASMS: Edited by Reinhard Dummer]

< Previous Article | Table of Contents | Next Article >

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Abstract

Purpose of review: Metastatic melanoma is the most aggressive skin cancer and despite tremendous efforts and considerable progress in clinical treatment of melanoma patients within recent years, it remains a deadly disease. Current treatments affect melanoma cells indiscriminately, while accumulating evidence suggests that melanoma might be a disease of stem cells. This review aims to summarize the important accomplishments in the field and to emphasize the common molecular and cellular mechanisms regulating self-renewal of neural crest stem cells (NCSCs) and melanoma cells.

Recent findings: A growing number of publications highlight the existence of phenotypic and functional similarities between embryonic NCSCs and melanoma cells. These studies provide compelling evidence that the propagation of melanoma cells critically depends on genes instrumental in neural crest

Outline

development. The example of *Sox10* and *Rac1* genes provides detailed illustration of how interfering with these important genes for neural crest development can prevent melanoma formation.

Summary: The development of new therapies, targeting RAF-MEK-ERK pathway, provided major improvements in outcomes for patients with metastatic melanoma; however, acquired resistance followed by tumor recurrence represents a major clinical challenge. The striking parallels between embryonic NCSCs (eNCSCs) and melanoma cells might lead to the development of new targeted therapeutics selectively eliminating cell populations accountable for tumor initiation, progression and relapse.

Back to Top

INTRODUCTION

Melanoma is a highly heterogeneous tumor and, in addition to melanocytes, is often composed of cells with neuronal, glial, chondrocytic and adipocytic features [1–4]. Several recent publications [5–7] strongly suggest that melanoma contains cells with neural crest-like characteristics, which are able to sustain the tumor growth and give rise to distant metastases *in vivo*. Recent functional studies provide compelling evidence that interfering with the maintenance of neural crest stem cells (NCSCs) by either applying chemical compounds suppressing neural crest development [8] or by deregulating genes crucial for the self-renewal of embryonic NCSCs (eNCSCs) [9[black small square],10[black small square]] leads to a profound suppressive effect on melanoma propagation *in vitro* and *in vivo*.

Back to Top

THE ROLE OF NEURAL CREST STEM CELLS IN EMBRYONIC AND ADULT TISSUE HOMEOSTASIS

Figure 1

Neural crest cells represent a transient and highly migratory embryonic cell population, characterized by multipotent and self-renewal capacities [11]. During embryonic development, NCSCs give rise to a plethora of different cell types including glia, neurons, smooth muscle cells, adipocytes, osteoblasts, chondrocytes and melanocytes (Fig. 1). For a long time it was generally accepted that NCSCs exist only in the developing embryo, but a groundbreaking study by Kruger and colleagues [12] demonstrated that cells with neural crest features similar to the one of eNCSCs reside in the adult gut. This finding triggered a number of studies, which identified the presence of postmigratory NCSCs in a variety of adult organs such as dorsal root ganglia [13,14], heart [15,16], carotid body [17], cornea [18,19], bone marrow [14], dental pulp and periodontal ligament [20,21], and skin [22–27]. Despite a substantial number of reports on the existence of adult NCSCs in the adult tissues, the physiological role of these cells remains poorly understood.

FF1_113_18_0_Figure 1 FIGURE 1. The embryonic neural crest cells. Neural crest cells arise in the ectoderm at the margins of the neural tube and, after extensive migration, settle down in different parts of the body giving rise to a variety of derivatives including melanocytes, neurons, glial cells, smooth muscle cells, adipocytes, osteoblasts and chondrocytes.

A recent report by the Miller group [28[black small square][black small square]] describes, for the first time, the role of neural crest precursor cells in wound healing in the adult mouse skin. Previously, Miller and colleagues identified multipotent, self-renewing cells residing in the adult skin and named these stem cells skin-derived precursor (SKP) cells [22]. The subsequent research demonstrated that SKPs exhibit neural crest-like features, as revealed by the expression of neural crest markers and their differentiation potential [23]. Moreover, genetic lineage tracing using *Wnt1-Cre R26R* mice identified SKPs as cells derived from the neural crest lineage [23]. The observations that the presence of innervation is crucial for organ regeneration in amphibians [29] and that neural crest-derived Schwann cells provide signals for successful tissue repair, prompted Miller and colleagues to investigate whether the cells associated with the nerve terminals surrounding the bulge area of the hair follicle might play an essential role in mammalian tissue repair. They demonstrated that these nerve terminal-associated cells expressed the transcription factor Sox2 together with other markers of neural crest cells such as $p75^{NTR}$, nestin and S100[beta] [28[black small square][black small square]]. Following wounding of the skin, some Sox2-positive cells started to proliferate and migrated into the regenerating dermis. Moreover, the genetic ablation of *Sox2* resulted in a significantly decreased rate of wound closure, providing crucial evidence that the presence of Sox2-positive neural crest-derived cells is essential for the successful repair of injured skin. Given the similarities between wound healing and cancer development, it is intriguing to think that NCSCs in addition to the newly established role in wound healing, might play a pivotal role in the initiation and maintenance of cancers such as melanoma.

Back to Top

COMMON GENE NETWORKS LINK MELANOMA WITH EMBRYONIC NEURAL CREST CELLS

The fact that in recent years, the number of studies dissecting remarkable parallels between self-renewal of NCSCs and melanoma cells is significantly growing, suggests that the understanding of the molecular and cellular mechanisms underlying NCSC biology might lead to novel approaches for the improvement of melanoma therapies. The substantial knowledge of gene regulatory networks controlling self-renewal of classical eNCSCs is prompting investigation into the role of molecules crucial for the maintenance of eNCSCs; however, several recent reports address the role of factors important to sustain also postmigratory targets of neural crest cells.

A prime example of a gene crucial for the self-renewal of eNCSCs is *Sox10*, a transcription factor that belongs to the Sox [Sry (sex determining region Y)-related HMG box] genes family, playing key roles in embryonic development and in the regulation of stem cell activity in various tissues [30]. *Sox10* is expressed throughout embryonic neural crest development and it was identified as the gene mutated in *Dom* mice (Dominant megacolon). Considering that Sox10 governs cell fate decisions during embryonic development, it is therefore not surprising that Sox10 haploinsufficiency causes Waardenburg Hirschsprung syndrome, characterized by a ganglionic megacolon due to the loss of ganglion cells, pigmentary abnormalities due to the lack of melanocytes and often deafness due to the loss of sensory innervation (Table 1) [9[black small square],10[black small square],31,32,33[black small square][black small square]].

Table 1

TT1_114_23_0_Table 1 Table 1 The role of Sox10 in different neural crest-derived cells during embryonic and postnatal development, giant congenital naevi and melanoma formation

Genetic studies established that Sox10 is critical for self-renewal and the survival of NCSCs during embryonic development [34,35]. Mouse embryos homozygous for the *Sox10*^{Dom}mutation entirely lack neural crest-derived melanocytes, it still remains unclear, however, whether this effect is due to the lack of NCSCs, giving rise to committed melanoblasts or, alternatively, due to the decreased survival of committed melanocytic progenitors [35,36]. Until recently, perinatal lethality resulting from disruption of *Sox10* gene precluded the analysis of the Sox10 role in a cell type-specific manner; however the generation of a conditional allele of Sox10 permitted such analysis [32]. A recent study by Harris *et al*.[33[black small square][black small square]] established that Sox10 is also crucial to sustain the melanocytic lineage in the adult murine skin (Table 1). Melanocytic lineage in the trunk skin is composed of two cell populations, located within the hair follicle and separated based on their anatomical location: the melanocyte stem cells which reside in the bulge region, and the differentiated melanocytes occupying the hair follicular bulb [37]. Functional disruption of the melanocyte stem cells leads to hair graying due to their inability to generate differentiated melanocytes [38]. The homozygous ablation of *Sox10* in the postnatal melanocytic lineage using a *Tyr-CreERT2* mouse line induces hair graying, accompanied by the lack of the differentiated melanocytes in the hair follicular bulb and the permanent reduction in the number of bulge-associated melanocyte stem cells (Table 1). Surprisingly, similar to *Sox10* knockout mice, *Sox10* overexpressing transgenic mice exhibit hair graying, suggesting that the levels of Sox10 expression are essential for the normal physiology of melanocyte stem cells [33[black small square][black small square]].

In addition to the role of Sox10 in the normal melanocytic lineage, we have recently highlighted the role of Sox10 in pathological melanocytic lesions, such as giant congenital naevi, and melanoma (Table 1) [9[black small square]]. We demonstrated that the vast majority of human and mouse giant congenital naevi and melanoma expressed SOX10 and that Sox10 expression is regulated by *Nras*^{Q61K}oncogene. To investigate the role of Sox10 in melanoma *in vivo*, we have used the *Tyr::Nras*^{Q61K}*Ink4a*$^{-/-}$mouse model of melanoma and showed that *Sox10* haploinsufficiency completely prevented the formation of giant congenital naevi and melanoma without affecting the normal functions of neural crest derivatives (Table 1). To address whether *Sox10* haploinsufficiency can also interfere with already established naevi, we have made use of conditional allele of *Sox10*[32]. *Sox10* loss in the skin of *Tyr::Nras*^{Q61K}mice resulted in the complete abolishment of Nras^{Q61K}-induced hyperpigmentation and subsequent naevi formation, suggesting that interfering with Sox10 levels can be beneficial for the patients with giant congenital naevi, who have an increased risk of melanoma formation. Furthermore, we have silenced SOX10 expression in established human melanoma cell lines and observed that melanoma cells displayed decreased proliferation, increased apoptosis and aberrant differentiation, effects strikingly resembling the effects of *Sox10* deletion in eNCSCs, and ultimately leading to the death of the cancer cells [9[black small square]]. Recently, another study examined the role of Sox10 in melanoma pathogenesis (Table 1) [10[black small square]]. Similarly to our findings, Pavan and colleagues demonstrated the requirement of Sox10 for the proliferation of melanoma cells *in vitro* and *in vivo. Sox10* haploinsufficiency reduced the number of pigmented naevi and delayed melanoma formation in the *Grm1*^{Tg}(glutamate receptor) mouse model for melanoma (Table 1) [10[black small square]]. Mechanistically, *SOX10* knockdown resulted in decreased levels of the transcription factor E2F1 and retinoblastoma protein (Rb), key components of the cell cycle progression, regulating the progression through the G_1 phase of the cell cycle [10[black small square]]. Moreover, the expression of CDK inhibitors, p21 and p27 were increased upon *SOX10* knockdown, suggesting that SOX10 regulates cell proliferation and cell cycle progression via multiple, convergent pathways. Taken together, these studies suggest that Sox10 might be a promising therapeutic target for the treatment of giant congenital naevi and melanoma.

In contrast to Sox10, which orchestrates both embryonic and adult neural crest-derived stem cell populations, Rac1 is an example of a molecule whose functions are restricted to the maintenance of postmigratory NCSCs [39]. Rac1 is a member of the Ras-related Rho family of small guanosinetriphosphatases (GTPases) and is involved in many cellular processes such as proliferation, actin cytoskeletal rearrangements, survival and invasiveness [40]. *Rac1*-deficient NCSCs display impaired cell cycle control, reduced proliferation and self-renewal and as a consequence, give rise to neural crest-derived structures reduced in size [39]. Embryos lacking *Rac1* are characterized by severe defects in the craniofacial and peripheral nervous system development [39,41]. Interestingly, *Rac1* deletion selectively affects postmigratory NCSCs, whereas neural crest cells emigrating from the neural tube do not depend on Rac1 function.

Recently, the identification of an activating mutation in the *RAC1* gene (*RAC1*^{P29S}) was described in about 10% of human melanoma samples and is the third most frequent mutation in human melanoma after those of *NRAS* and *BRAF*[42[black small square],43[black small square]]. In a recent study Machesky and colleagues addressed the role of *Rac1* in the *Tyr::Nras*^{Q61K}*Ink4a*$^{-/-}$ mouse model of melanoma *in vivo* and showed that *Rac1* functions downstream of *Nras*^{Q61K}and that the genetic ablation of *Rac1* resulted in a decreased number of melanocytes and led to pigmentation defects in the skin [44[black small square]]. Importantly, pharmacological inhibition of Rac1 using Rac-specific inhibitors (NSC23766 and EHT1864) resulted in a significantly reduced proliferation of *Nras*^{Q61K}melanoma cells [44[black small square]]. Previous studies showed that the *Rac1*^{V12} mutation, which induces a constitutive activation of Rac1, leads to anchorage-independent growth in soft agar and is able to induce tumors *in vivo* upon transplantation in immunocompromised mice [45], suggesting that *V12Rac1* can act as an oncogene. However, the expression of constitutively active *RAC1*^{V12}in zebrafish *in vivo* is neither sufficient to induce melanoma formation alone, nor cooperates with *BRAF*^{V600E}, but accelerates *HRAS*^{V12}-induced melanoma nodule formation *in vivo*[46]. It is somewhat puzzling that *RAC1*^{V12} is not sufficient to induce melanoma formation in zebrafish *in vivo*, whereas the *RAC1*^{P29S}mutation leads to increased proliferation and migration of cultured melanocytes [42[black small square],46]. Taken together, these findings identify Rac1 as a potential novel candidate target for melanoma therapy. Studies of the role of RAC1 in other cancer types, such as breast [47], colorectal [48], testicular [49], gastric [50], cervical [51], and nonsmall cell lung cancer [52] might help to unravel the precise molecular mechanisms underlying *RAC1* function in melanoma.

Back to Top

CANCER STEM CELLS IN TUMOR PROGRESSION: IN-VIVO LINEAGE TRACING

One of the most exciting concepts in cancer biology over the last several years is that cancer might be a disease of stem cells. Although various studies have attempted to address this issue in melanoma, the results remain controversial and await further experimental validation. The recent studies in the field of melanoma research relied on the isolation of a specific subpopulation of cancer cells based on the expression of specific cell-surface markers followed by transplantation into immunocompromised mice [6,53,54]. There are a number of limitations of such experimental setup, namely the destruction of the endogenous microenvironment, the lack of supporting niche due to the transplantation of melanoma cells into the subcutaneous layer of the skin, and the lack of the immune system, all conditions ultimately changing the behavior of cancer cells [55]. Transplantation experiments assess therefore the potential of cancer cells to form tumors rather than following the fate of cancer cells in their natural environment. The emergence of recent novel experimental strategies in other types of cancers might provide an interesting opportunity for future experiments also in the melanoma field. Tracking tumor cells *in vivo* using genetic approaches has become experimentally possible as demonstrated by three independent groups last year [56[black small square][black small square]–58[black small square][black small square]]. The results obtained for tumors of the skin, the brain and the gut provide the evidence that a small subset of cancer cells sustains tumor growth and importantly that, by specifically targeting these rare cells, cancer can be cured. Parada and colleagues evaluated the role of Nestin-positive cells in sustaining the growth of glioblastoma, the most aggressive brain tumor [57[black small square][black small square]]. Using a genetically engineered mouse model of glioma, they could show that the selective eradication of Nestin-positive cells resulted in the increased survival of glioblastoma mice and moreover, Nestin-expressing cells were responsible for the glioblastoma relapse after treatment with temozolomide. In another study, Clevers and colleagues addressed whether Lgr5 (leucine-rich repeat-containing heterotrimeric guanine nucleotide-binding protein-coupled receptor 5), a marker of adult stem cells in the intestinal crypt, labels the cells sustaining the growth of intestinal adenomas [58[black small square][black small square]]. Using the multicolor reporter mouse *R26R-Confetti*, which allows to label and to distinguish individual intestinal cells, Schepers *et al.*[58[black small square][black small square]] showed that Lgr5-positive cells not only self-renew and give rise to new Lgr5-positive cells within adenomas but also generate all other adenoma cell types. Finally, Blanpain and colleagues tested the concept of cancer stem cells in mouse models of skin papilloma and invasive squamous cell carcinoma [56[black small square][black small square]]. In benign skin papilloma, genetic lineage tracing and clonal analysis of individual tumor cells at different stages of tumor progression revealed the existence of two distinct cell populations, the fast cycling fraction with limited self-renewal and the slow cycling subpopulation with stem cell-like features. In contrast to benign tumors, a single cell population, generating highly undifferentiated tumorigenic clones, sustained invasive squamous carcinoma. The future research will need to address the unique characteristics of cancer stem cell populations in order to eradicate the cells responsible for tumor propagation.

Back to Top

CONCLUSION

Future studies are needed to determine the expression profile of melanoma stem cells versus normal NCSCs and the identification of the markers exclusively expressed by melanoma stem cells. A major challenge will be to selectively eliminate the NCSCs maintaining melanoma growth and progression without affecting the pool of normal NCSCs required to sustain healthy tissue homeostasis. In particular, Sox10 haploinsufficiency might serve as a good example of such strategy because it completely abolishes melanoma formation without affecting neural crest derivatives in the healthy tissue.

Back to Top

Acknowledgements

None.

Back to Top

Conflicts of interest

There are no conflicts of interest.

Back to Top

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

[black small square] of special interest

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Back to Top

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Here we show that the neural crest transcription factor Sox10 is expressed in the vast majority of giant congenital naevi and melanoma samples. We demonstrate that Sox10 expression is regulated by $Nras^{Q61K}$ oncogene. Sox10 haploinsufficiency prevents melanoma formation without affecting the physiological functions of neural crest derivatives. SOX10 silencing in human melanoma cells affected cell-cycle progression, cell survival and completely abolished in-vivo tumor formation. Taken together, these results suggest that SOX10 represents a novel therapeutic target for melanoma therapy.

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55. Shakhova O, Sommer L. Testing the cancer stem cell hypothesis in melanoma: the clinics will tell. Cancer Lett 2012; 338:74–81. [Context Link]

56[black small square][black small square]. Driessens G, Beck B, Caauwe A, et al. Defining the mode of tumour growth by clonal analysis. Nature 2012; 488:527–530. SFX | [Context Link]

Using genetic lineage tracing and clonal analysis, the authors analyzed benign skin papillomas and invasive skin carcinomas for the presence of cancer stem cells. Invasive squamous carcinomas were sustained by a single fast proliferating cell population, displaying limited differentiation potential.

57[black small square][black small square]. Chen J, Li Y, Yu TS, et al. A restricted cell population propagates glioblastoma growth after chemotherapy. Nature 2012; 488:522–526. SFX | [Context Link]

In this study, the authors generated a mouse model, which allows to specifically eliminate Nestin-positive cells in tumor-bearing mice by utilizing ganciclovir. Sequential administration of temozolomide and ganciclovir resulted in the efficient depletion of tumors. Importantly, authors demonstrate that only cancer stem cells sustain tumor formation and are responsible for tumor recurrence in this model.

58[black small square][black small square]. Schepers AG, Snippert HJ, Stange DE, et al. Lineage tracing reveals Lgr5+ stem cell activity in mouse intestinal adenomas. Science 2012; 337:730–735. SFX | [Context Link]

Lineage tracing using the R26R-Confetti multicolor reporter line allowed the authors to trace individual cells within intestinal adenomas. They demonstrate that Lgr5-expressing cells have the capacity to self-renew, give rise to the other cell types in adenomas and sustain tumor growth *in vivo*.

Keywords: cancer stem cells; melanocytes; melanoma; neural crest stem cells

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IMAGE GALLERY

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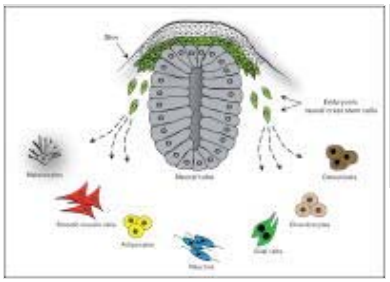

Figure 1

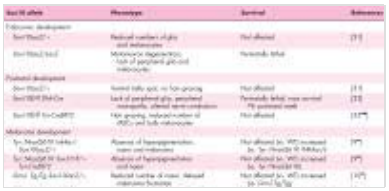

Table 1

Back to Top

< Previous Article | Table of Contents | Next Article >